Is there a causal linkage between cannabis use and increased risks of psychotic symptoms?

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Macleod and Hickman (1) focus on the relationships between cannabis and schizophrenia and dismiss research examining the linkages between cannabis and symptom measures on the grounds that the linkage between symptom levels and clinical outcomes is not known. While this focus favours the arguments they develop, it does not adequately represent the literature that they claim to be reviewing. The focus of this literature has not been on the specific linkages between cannabis and schizophrenia, but rather on whether the use of cannabis increases rates of psychotic symptoms (2).

Macleod and Hickman propose that any link between cannabis use and psychotic symptoms could be explained by residual confounding or reverse causation. Because of their focus on schizophrenia, they minimise recent research that has examined these issues using symptom measures. This evidence has been examined in a number of recent reviews (2-8) all of which have concluded that the weight of the evidence favours the view that the associations between cannabis and increased rates of psychotic symptoms are likely to be causal. Perhaps the most comprehensive review of this evidence is provided by Moore et al (4), who noted that that the findings of associations between cannabis and psychotic symptoms have been replicated by a series of 7 cohort studies in which: a) about 60 confounding factors have been controlled; b) one study controlled non-observed confounding; and c) in all studies reverse causality had been controlled. All studies produced evidence consistent with the view that there is a modest association between increasing use of cannabis and increased rates of psychotic symptoms. Further, as Hall has pointed out (3), these findings are supported by these additional lines of evidence: laboratory findings in animals; double-blind provocation research with people with schizophrenia; and by evidence of gene x environment interactions.

Although all of this evidence could be dismissed on the grounds of inappropriate measurement, failure to control residual confounding and reverse causality, such arguments are neither parsimonious nor compelling. In order to sustain their position that cannabis may not be

causally to related to psychosis/psychotic symptoms, Macleod and Hickman have to engage in a increasingly elaborate set of arguments which: a) focus the debate exclusively on schizophrenia rather than psychotic symptoms; b) dismiss recent studies that have extensively controlled confounding and reverse causality; and c) discount evidence of underlying biological mechanisms. As Macleod and Hickman note, their arguments are largely underwritten by analogy with "several recent studies much more methodologically robust than those relating to cannabis use to psychosis, which have led to some of the most important mistakes in recent epidemiological history". The issue to which they refer concerns the discrepancies between observational studies and randomised trial findings in the area of hormone replacement therapy (HRT) (9). In that area, observational studies suggested positive benefits in reducing coronary heart disease, whereas randomised control trials led to the opposite conclusion. Here is not the place to review this literature, but two points are worth making. The first is that the discrepancy between randomised controlled trials and observational studies for the HRT and CHD was an exception to the general rule that the conclusions of observational studies have been found to be consistent with RCTs (10, 11). Second, an examination of the reasons for observational studies of HRT producing misleading findings appears to have been due to a failure to adequately control socio-economic factors (9). These limitations in the assessment of confounders do not apply to the literature on cannabis and psychotic symptoms.

In summary, while it remains possible that associations between cannabis and psychotic symptoms are non-causal and can be explained away as a result of inadequate measurement, residual confounding and reverse causation, the weight of the evidence including observational research, animal studies, laboratory research and behavioural genetic research all points to a causal process in which increasing use of cannabis is associated with small but detectable increases in the risks of psychosis and psychotic symptoms. While the HRT example posts a warning about the pitfalls of causal reasoning with observational evidence, this example is, in fact, an exception to the general rule that the findings of well-conducted observational research are usually consistent with

the findings of well-conducted randomised trials. Despite Macleod and Hickman's reservations, a growing number of well-conducted observational studies suggest the presence of a causal link between increasing use of cannabis and increasing rates of psychosis/psychotic symptoms.

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